HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

201-16139

TEST PLAN
For
Trimethyl phosphite
(TMP)
CAS No. 121-45-9

Submitted to the US EPA
By
Trimethyl Phosphite Consortium.

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1 INTRODUCTION

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program, the Trimethyl Phosphite Consortium, voluntarily commits to compile basic screening data on:

- Phosphorus Acid, Trimethyl Ester
  CAS No. 121-45-9

This test plan follows up on the commitment. Specifically, this test plan sets forth how the Trimethyl Phosphite Consortium intends to address testing information for Trimethyl Phosphitwe.

In preparing the test plan the following steps were undertaken:

Step 1: A search was conducted for relevant published and unpublished literature on Trimethyl Phosphite.

Step 2:The compiled data was evaluated for adequacy in accordance with the EPA guidance documentation.

2 GENERAL SUBSTANCE INFORMATION

Chemical name: Trimethyl phosphite

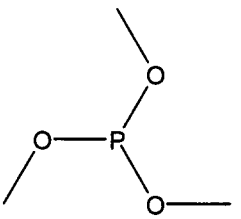
CAS No: 121-45-9

Synonyms: Phosphorous acid, trimethyl ester - Trimethoxyphosphine - TMP

Molecular formula: $C_3 H_9 O_3 P_1$

Molecular weight: 124.08

Structural diagram:



3 USE AND EXPOSURE INFORMATION

The subject chemical is used as a chemical intermediate in the manufacture of other phosphorus containing molecules. Trimethyl Phosphite is primarily manufactured overseas and imported into the USA for domestic market use. The downstream phosphorus-containing products produced from Trimethyl Phosphite may be used in a variety of applications including crop protection products, flame retardant chemicals and lubricant additives. Trimethyl Phosphite is typically fully reacted in the manufacture process with downstream products only containing trace residuals. As a chemical intermediate used in closed systems at chemical manufacturer sites, there will be limited potential for occupational exposure to the chemical at either manufacturer or user sites. Trimethyl Phosphite has a strong unpleasant odor with a reported odor threshold of 0.0001 parts per million. The additional engineering controls used to control odors further minimize occupational exposure.

4 REVIEW OF EXISTING DATA AND DEVELOPMENT OF TEST PLAN

The member companies have undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for TMP.

The more significant and reliable data are gathered in table n° 6. The availability of the data on the specific SIDS endpoints is summarized in table n° 7.

4.1 Review of existing physicochemical data and proposed testing

Melting point, boiling point and vapor pressure values are available in standard data sources and are consistent with calculated values.

TMP hydrolyzes rapidly in water (see section 4.2). An octanol-water partition coefficient and a water solubility value cannot be generated experimentally. Estimations can be obtained with the KOWWIN and WSKOW programs.

No additional testing is proposed for the purposes of the HPV program.

4.2 Review of existing environmental fate data and proposed testing

– *Photodegradation*

A lifetime of 0.4 hour has been measured in dry air with OH radicals at an average 24-hour concentration of 10^6 molecules/cm^3. Trimethyl phosphate is the major degradation product.

An estimated half-life of 1.3 days is obtained with the AOP program considering an OH radical concentration of $1.5x10^6$ molecules/cm^3 for 12 hours per day.

– *Stability in water*

Three hydrolysis studies of reliability (2) are available on TMP (cf. Table n° 1). These studies show that TMP is rapidly hydrolyzed to dimethyl phosphonate (DMHP) and methanol. Dimethyl phosphonate is further hydrolyzed to monomethyl phosphonate (MMHP) and methanol with a lower hydrolysis rate (cf. Table n° 1). Monomethyl phosphonate hydrolyzes slowly to phosphorous acid and methanol.

No further testing is proposed for this endpoint.

Table n° 1: Hydrolysis properties of TMP, DMHP and MMHP

Substance	Result	Method	Source
TMP CAS No 121-45-9	DT50 = 21 min at pH 10 and 25°C DT50 < 5 min at pH 6 and 0°C	In a two phase system (pentane/water), TMP initially introduced in the organic phase	Johnston, 1981 (Mobil Chemical Co.)
	100% hydrolysis after 0.5 h	In pure water, no control of pH (preliminary stability test prior to a fish acute toxicity test)	Bayer, 1992
	DT50= 8-9 min at 25 °C	In pure water	Arbuzov et al., 1957
DMHP CAS No 868-85-9	DT50 = 470 h (19.6 d) at pH 4 at 23°C DT50 = 3 h at pH 7 at 23°C DT50 < 0.3 h at pH 9 at 23°C	OECD 111	Bayer, 2002
	DT50 ca. 60h	In pure water, no control of pH (preliminary stability test prior to a fish acute toxicity test)	Bayer, 1992
	DT50 = 10.8 d at 25°C	In water, preliminary neutralized	Belskii et

			al.,1969
MMHP	Hydrolyzes slowly	In pure water, no control of pH (preliminary stability test prior to a fish acute toxicity test)	Bayer, 1992

– *Biodegradation*

Biodegradation data are not available on TMP. However TMP is rapidly hydrolyzed to DMHP (cf. hydrolysis studies above). A ready biodegradation study of reliability (1) is available on DMHP which shows that DMHP is not readily biodegradable (50 % biodegradation after 28 days in an OECD 301 E test, Bayer, 1992). Therefore TMP can be considered as not readily biodegradable and **no further testing is proposed for this endpoint.**

– *Transport and distribution*

As TMP is rapidly hydrolyzed to DMHP in presence of water, a level III fugacity modeling has been performed on DMHP with the EPIWIN program.

EPIWIN estimated physicochemical and fate data were used, except for the vapor pressure. A reliable experimental data of 1.35 hPa at 20°C (Bayer, 2001) has been used.

DMHP is shown to distribute mainly in water and soil when discharged equally in air, water and soil. When discharged solely in water or soil, DMHP remains mainly in the original receiving compartment with significant transfer to the soil or water compartment. When discharged in air, DMHP remains mainly in air with significant transfers to the soil and water compartments.

4.3 Review of existing ecotoxicity data and proposed testing

Toxicity studies on fish, algae and daphnia are not available on TMP. However TMP is rapidly hydrolyzed to DMHP and toxicity studies of reliability (1) on fish, algae and daphnia are available on DMHP (cf. Table n°2). **Therefore no further aquatic toxicity testing is proposed for purposes of the HPV program.**

Table n° 2: Most relevant ecotoxicity data on DMHP

Endpoint	Substance	Result	Method	Source
Acute toxicity to fish	DMHP	96h-LC0 ≥ 100 mg/l (nominal)	OECD 203	Bayer, 1992
Acute toxicity to daphnia	DMHP	48h-EC50 = 25 mg/l (nominal)	OECD 202	Bayer, 2003a
Toxicity to algae	DMHP	72h-EC0 ≥ 100 mg/l (nominal)	OECD 201	Bayer, 2003b

4.4 Review of existing toxicity data and proposed testing

– *Acute Toxicity*

A number of acute oral toxicity studies of reliability (2) in the rat are available on TMP (cf. Table n° 3), with consistent results. A conservative estimate of the rat oral LD50 is 1350 mg/kg bw. The mouse appears to be less sensitive, with an oral LD50 of 4280 mg/kg bw. The rabbit dermal LD50 is 934 mg/kg bw. The rat 1 hour inhalation LC50 is 182 mg/l, while inhalation for 4 hours was not lethal at 9000 ppm (45.7 mg/l). For both inhalation studies, stated concentrations were based on quantity of substance used, so may overestimate the actual exposure concentration. All the acute studies were conducted before the introduction of GLP guidelines, however the results are consistent, leading to the conclusion that TMP is of moderate acute toxicity. A study of cholinesterase inhibition following intravenous administration of TMP in rats, rabbits and dogs and in vitro studies of cholinesterase inhibition potential demonstrated that TMP does not have any significant specific cholinesterase inhibition potential. **Therefore no further acute toxicity testing is proposed for purposes of the HPV program.**

Table n° 3: Most relevant acute toxicity data on TMP

Endpoint	Substance	Species	Result	Method	Source
Acute oral toxicity	TMP	Rat	LD50 = 1350 mg/kg bw	Other	Ebbens, 1973
		"	LD50 = 1500 mg/kg bw	"	Terrell, 1976
		"	LD50 = 1595 mg/kg bw	"	Terrell, 1976
		"	LD50 = 1640 mg/kg bw	"	Terrell, 1976
		"	LD50 = 1970 mg/kg bw	"	Terrell, 1976
		"	LD50 = 2000 mg/kg bw	"	Terrell, 1976
		"	LD50 = 2000 mg/kg bw	"	Terrell, 1976
		"	LD50 = 2240 mg/kg bw	"	Terrell, 1976
		Mouse	LD50 = 4280 mg/kg bw	"	Terrell, 1976
Acute inhalation toxicity	TMP	Rat	1h LC50 = 182 mg/l (nominal)	Other	Zeigler, 1977
		"	4h LC50 > 45.7 mg/l (9000ppm) (nominal)	"	Gabriel, 1969
Acute dermal toxicity	TMP	Rabbit	LD50 = 934 mg/kg bw	Other	Ebbens, 1973
		"	LD50 = 7500 mg/kg bw	"	Becker, 1976
Acute dermal irritation	TMP	Rabbit	Slightly irritating	Other	Becker, 1976
Acute eye irritation	TMP	Rabbit	Slightly irritating	Other	Becker, 1976
Serum cholinesterase inhibition	TMP	Rat	No significant inhibition	Other	Munson, 1979
		Rabbit	"	"	"
		Dog	"	"	"
		In vitro (rat)	"	"	Dramlia, 1981
			"	"	Meeks, 1979

- *Repeat Dose Toxicity*

Effects of repeated exposure to TMP have been characterised in studies of reliability (2) for all relevant routes of exposure (cf. Table n° 4).

A 90-day oral gavage study in rats showed mortality and significant intermittent reduction in bodyweight gain at 160 mg/kg/day, with testicular hypoplasia and reduced spermatogenesis (spermatogonia and other spermatogenic cells reduced in size and number) at the same dose in males. However, the density of sperm in the epididymis was not greatly or uniformly reduced. No significant effects were observed at 80 mg/kg bw/day.

A dermal toxicity study in which rabbits were exposed for 6 hours per day for 21 days (both abraded and non-abraded sites) showed dose-related irritancy, with mortality and effects on lungs and liver, which may have been secondary to irritancy. The LOAEL for this study was 300 mg/kg bw/day.

A 28-day inhalation study in rats showed cataracts and effects on the lungs. Although they were both considered likely to be related to viral disease in the animals, two further studies were carried out to elucidate the effect. The conclusion from the three studies was that TMP was cataractogenic and a corneal irritant at concentrations from 50 ppm. There was some reversibility at this concentration and at 100 ppm, but cataracts seen at 600 ppm were irreversible. No lenticular or corneal damage was seen at 10 ppm. Inflammatory effects in the lungs at 600 ppm were likely to have resulted from exacerbation of pre-existing pneumonitis.

An early (1971) 8-week inhalation study in rats, at the single nominal concentration of 500 ppm, showed histopathological changes in the lungs (interstitial pneumonitis, increased number of mucus-producing goblet cells in bronchial mucosa, squamous metaplasia of alveoli plus tumorlets extending into, or filling, the alveolar spaces, pulmonary vascular sclerosis and emphysematous changes). These were considered to be likely to represent potential for serious irreversible lung damage, including pre-cancerous changes. Effects on the skin (hyperkeratosis; parakeratosis; acanthosis; focal folliculitis, infiltration of inflammatory cells) were considered less important and due to irritation. No histopathological effects on the testes were reported, and spermatogenesis was stated to be active.

A later review of this study concluded that the interpretation of the lung effects was unreliable. Changes seen were considered likely to be related to chronic lung disease in the laboratory rats. Also, no precautions had been taken in the study to avoid hydrolysis of TMP to dimethyl hydrogen phosphite (DMHP), monomethyl phosphite and ultimately to phosphorous acid (see Stability in water, above) A carcinogenicity assay on DMHP in rats has concluded that there was clear evidence for carcinogenicity in male rats and equivocal evidence in female rats. The lung tumours seen in this DMHP study (dose-related squamous cell carcinomas, and alveolar/bronchiolar adenomas or carcinomas) are consistent with the changes seen in the 8-week "TMP" study. No significant lung changes were seen in the series of 28-day studies conducted on TMP protected from hydrolysis by a nitrogen blanket. If the effects in the 8-week study are substance-related, then it is considered that they relate to the hydrolysis product, not to TMP. No evidence of carcinogencity was seen in a carcinogenicity study on DMHP in the mouse.

Therefore no further repeated dose toxicity testing is proposed for purposes of the HPV program.

Table n° 4: Most relevant repeated dose toxicity data on TMP

Endpoint	Substance	Species	Result	Method	Source
21-day Oral	TMP	Rat	NOAEL: 32.8 mg/kg/d	Other	Rabold, 1977
90-day Oral	TMP	Rat	160 mg/kg/d: Testicular hypoplasia, reduced spermatogenesis. NOAEL: 80 mg/kg/d bw	Other	Klopp, 1977
21-day Dermal	TMP	Rabbit	300/600/1200 mg/kg/d: dose-related mortalities, irritation, effects on lungs and liver. LOAEL: 300 mg/kg/d bw	Other	Becker, 1977
28-day Inhalation	TMP	Rat	1) 581 ppm inflammatory changes in lung. 292/581 ppm: Cataracts NOAEL: 104 ppm	Other	Rusch, 1979
		Rat	2) 105 ppm Reversible lenticular opacities 600 ppm: Irreversible cataracts LOAEL: 105 ppm	"	Rusch, 1979
		Rat	3) 50/101 ppm Reversible lenticular opacities, irregular corneal surfaces. NOAEL: 10 ppm	"	Rusch, 1979

– *Genetic Toxicity in vitro and in vivo*

The genotoxicity of TMP has been examined in a battery of *in vitro* and *in vivo* assays of reliability (2) (cf. Table n° 5). Several of the *in vitro* studies for gene mutation indicate that TMP has mutagenic potential. However, no mammalian *in vivo* studies on his endpoint or on chromosomal aberration are available. The significance of the studies in Drosophila is uncertain. **Therefore it is proposed to conduct a micronucleus test, OECD 474, to satisfy this endpoint for purposes of the HPV program.**

Table n° 5: Most relevant genotoxicity data on TMP

Endpoint	Sub-stance	Test system	Activ-ation	Result	Method	Source
Bacterial mutagenicity in vitro	TMP	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	±	Negative	Other	Haworth, 1979
Bacterial mutagenicity in vitro	TMP	S. typhimurium TA1535, TA100, TA1537, TA1538, TA98 S. cerevisiae D4	±	Negative	Other	Brusick, 1979
Mammalian mutagenicity in vitro	TMP	L5178Y/TK+/- mouse lymphoma cells	±	Positive	Other	Kirby, 1979
Mammalian	TMP	L5178Y/TK+/- mouse lymphoma cells	±	Positive	Other	Kirby, 1979

mutagenicity in vitro						
Mammalian mutagenicity in vitro	TMP	L5178Y/TK+/- mouse lymphoma cells	±	Positive	Other	Kirby, 1979
DNA damage & repair assay in vitro	TMP	E coli WP2/WP100, S. typhimurium TA1978/TA1538	±	Positive	Other	Haworth, 1979
DNA damage & repair assay in vitro	TMP	E coli WP2/WP100, S. typhimurium TA1978/TA1538	±	Positive	Other	Haworth, 1979
DNA damage & repair assay in vitro	TMP	E coli WP2/WP100, S. typhimurium TA1978/TA1538	±	Negative	Other	Haworth, 1979
Call transformation assay in vitro	TMP	C3H/10T½ CL8 cells		Negative	Other	Thilagar, 1979
In vivo Drosophila mutagenicity assay	TMP	Point mutations: 1) Sex-linked Lethals 2) White-ivory Somatic Reversions. Chromosome aberrations and loss: 1) Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis		 Negative " " " "	Other	Bowman, 1980
In vivo Drosophila mutagenicity assay	TMP	Point mutations: 1) Sex-linked Lethals 2) White-ivory Somatic Reversions. Chromosome aberrations and loss: 1) Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis		 Positive Negative Positive Negative Positive	Other	Bowman, 1980
In vivo Drosophila mutagenicity assay	TMP	Point mutations: 1) Sex-linked Lethals 2) White-ivory Somatic Reversions. Chromosome aberrations and loss: 1) Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis		 Positive Negative Positive Positive Positive	Other	Bowman, 1979

– *Carcinogenicity*

See discussion of effects in 8-week inhalation toxicity study, under repeat dose toxicity.

– *Toxicity to Reproduction*

Fertility
No dedicated study has been conducted on fertility. Testicular hypoplasia and reduced spermatogenesis were observed at 160 mg/kg/day in a 90-day oral gavage study in rats, but with little reduction in sperm density in the epididymis. Mortality and general toxicity (significant reduction in bodyweight gain) were also noted at this dose. No effects were seen at 80 mg/kg bw/day. Repeated dose studies by inhalation did not reveal any effects on the testes at up to 581 ppm (2.95 mg/l) for 28 days. No effects on male reproductive organs were seen in a 21-day dermal toxicity study at up to 600 mg/kg bw/day. No effects were seen on female reproductive organs in any of these studies. (see Repeat-dose toxicity, above). These findings are not considered to indicate a specific reproductive risk.

Development
A teratogenicity study by gavage in SD rats on days 6 through 15 of pregnancy showed teratologic effects at 164 mg/kg bw/day. Gross Abnormalities were exencephaly, spina bifida, scoliosis and cleft palate.

Skeletal abnormalities seen were primarily abnormalities of long bones. The incidence of abnormalities of sternebrae, rudimentary ribs and partial ossification of sternebrae and vertebrae was increased. Soft Tissue abnormalities seen at 164 mg/kg/day were a marked increased in dilated ventricles and in undescended testes. It was concluded that TMP was teratogenic during the period of major organogenesis at 164 mg/kg/day. Teratogenicity appears to be a direct result of exposure to TMP rather than secondary to maternal toxicity, which was seen only as a slight reduction in bodyweight gain. The maternal and foetal NOAEL in this study was 49 mg/kg/day.

Therefore no further reproductive toxicity testing is proposed for purposes of the HPV program.

– *Experiences with human Exposure (Work Place Exposure)*

Examination of the 180 employees at a TMP manufacturing plant, with varying degrees of exposure over a number of years showed no clinical cataracts in either the exposed (n=117) or non-exposed (n=63) employee groups. Numerous subclinical non-progressive congenital opacities and early progressive senile opacities were identified, with no association between TMP exposure and cataract formation. Analyses of workplace air indicated that average exposure in 1979 was between 0.3 and 4 ppm, with excursions to 15 ppm.

Female employees were questioned concerning pregnancy. Only one office worker had attempted conception, and had successfully conceived and delivered on three separate occasions. No male employees had been questioned. The sample was too small to draw any conclusions.

5 SUMMARY

In summary, the testing proposed in Table n° 7 will complete the data acquisition requirements for TMP under the U.S. Environmental Protection Agency High Production Volume (HPV) Chemical Challenge Program.

6 ROBUST STUDY SUMMARIES

An IUCLID Data Set for TMP is appended.

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Table n° 6: Significant Data on TMP

TMP CAS No 121-45-9		
Endpoint	**Result**	**Comment**
Physicochemical		
Melting point	-78 °C	Handbook data
Boiling point	111 °C at 1013 hPa	Handbook data
Density	1.046 at 20°C	Handbook data
Vapor pressure	32 hPa at 25°C	Handbook data
Log Pow	Hydrolyzes rapidly	Experimental data
	-0.73 at 25°C	Estimation
Water solubility	Hydrolyzes rapidly	Experimental data
	407 g/l at 25°C	Estimation
Environmental fate and pathway		
Photodegradation	Lifetime in air = 0.4 h	Experimental data
Stability in water	DT100 ≤ 0.5 h	Experimental data
Transport/distribution	Air = 5 %	Fugacity model level III performed
	Water = 53 %	on dimethyl phosphonate, the
	Soil = 42%	hydrolysis product of TMP, with
	Sediment = 0.09%	discharge in air, water and soil
Biodegradation	Not readily biodegradable	Experimental data on dimethyl phosphonate, the hydrolysis product of TMP
Ecotoxicity		
Acute fish	LC0 ≥ 100 mg/l (nominal)	Experimental data on dimethyl
Acute daphnia	EC50 = 25 mg/l (nominal)	phosphonate, the hydrolysis
Algae	LC0 ≥ 100 mg/l (nominal)	product of TMP
Toxicology		
Acute toxicity	Oral LD50: 1350 mg/kg (Rat)	Experimental data
	Dermal LD50: 934 mg/kg (Rabbit)	
	Inhalation LC50/1h: 182 mg/l (Rat)	
Repeated dose toxicity	NOEL cateractogenicity: 10 ppm	Experimental data
Genetic toxicity *in vitro*		Experimental data
Gene mutation	Overall, positive	
Chromosomal aberration		
Genetic toxicity *In vivo*		
Toxicity to reproduction	Possible reduced male fertility, NOEL 80 mg/kg/d	Experimental data
Developmental tox/teratogenicity	Teratogenic NOEL 49 mg/kg/d	Experimental data
Human experience	No cataracts	Clinical data

Table n° 7 : Availability of data and proposed testing on TMP

TMP CAS No 121-45-9							
Endpoint	**Available**	**GLP**	**OECD study**	**Other study**	**Estim. method**	**Accept-able**	**SIDS testing required**
Physicochemical							
Melting point	Y	N	N	Y	N	Y	N
Boiling point	Y	N	N	Y	N	Y	N
Density	Y	N	N	Y	N	Y	N
Vapor pressure	Y	N	N	Y	N	Y	N
Oct:water partition coef	Y	N	N	N	Y	Y	N
Water solubility	Y	N	N	N	Y	Y	N
Environmental fate and pathway							
Photodegradation	Y	N	N	Y	N	Y	N
Stability in water	Y	N	N	Y	N	Y	N
Transport/distribution	Y	N	N	N	Y	Y	N
Biodegradation	Y	Y	Y	N	N	Y	N
Ecotoxicity							
Acute fish	Y	Y	Y	N	N	Y	N
Acute daphnia	Y	Y	Y	N	N	Y	N
Algae	Y	Y	Y	N	N	Y	N
Toxicology							
Acute toxicity	Y	N	N	Y	N	Y	N
Repeated dose toxicity	Y	N	N	Y	N	Y	N
Genetic toxicity: Gene mutation - Bacterial (Ames test)	Y	N	N	Y	N	Y	N
– Mammalian (L5178Y Mouse lymphoma test)	Y	N	N	Y	N	Y	N
Chromosome aberrat.	Y	N	N	Y	N	N	Y
Toxicity to reproduction	Y	N	N	Y	N	Y	N
Devel. tox/terat	Y	N	N	Y	N	Y	N
Human experience	Y	N	N	Y	N	Y	N

Y : yes
N : no